

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074946

Trade Name : ACYCLOVIR TABLETS

Generic Name: Acyclovir Tablets 400mg and 800mg

Sponsor : Applied Analytical Industries, Inc.

Approval Date: November 19, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074946_____

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074946

APPROVAL LETTER

Applied Analytical Industries, Inc.
Attention: Jennifer Hutchison
Agent for: Aesgen, Inc.
1206 North 23rd Street
Wilmington, NC 28405
|||||

NOV 19 1997

Dear Ms. Hutchison:

This is in reference to your abbreviated new drug application dated August 19, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Tablets, 400 mg and 800 mg.

Reference is also made to your amendments dated April 22, 1997, May 7, 1997, June 17, 1997, August 7, 1997 and September 30, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Tablets, 400 mg and 800 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Tablets, 400 mg and 800 mg, respectively, of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074946

FINAL PRINTED LABELING

Each tablet contains 400 mg acyclovir, USP.
USUAL DOSAGE: See package circular for full prescribing information.
Dispense in a tight, light-resistant container, as defined in the USP.
Store between 15° and 25° C (59° and 77° F). Protect from light and moisture.
Manufactured for:

Aesgen_{INC}
Wilmington, NC 28403

By: **MOVA PHARMACEUTICAL CORPORATION**
Caguas, P.R. 00725, USA

ACYCLOVIR
Tablets

400 mg

**CAUTION: Federal law prohibits
dispensing without prescription.**

1000 Tablets

LOT #:

EXP. DATE:

6239100MV

ISSUED 5/96



N 3 55370-544-09 9

Each tablet contains 400 mg acyclovir, USP.
USUAL DOSAGE: See package circular for full prescribing information.
Dispense in a tight, light-resistant container, as defined in the USP.
Store between 15° and 25° C (59° and 77° F). Protect from light and moisture.

Manufactured for:
Aesgen_{INC}
Wilmington, NC 28403
By: **MOVA PHARMACEUTICAL CORPORATION**
Caguas, P.R. 00725, USA

ACYCLOVIR
Tablets

400 mg

**CAUTION: Federal law prohibits
dispensing without prescription.**

100 Tablets

NDC 55370-544-07

LOT #:

EXP. DATE:

6239200MV

ISSUED 5/96



N 3 55370-544-07 5

Each tablet contains 800 mg acyclovir, USP.
USUAL DOSAGE: See package circular for full prescribing information. Dispense in a tight, light-resistant container, as defined in the USP.
Store between 15° and 25° C (59° and 77° F). Protect from light and moisture.

Manufactured for:

Aesgen_{INC}
Wilmington, NC 28403

By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

A

ACYCLOVIR Tablets

800 mg

**CAUTION: Federal law prohibits
dispensing without prescription.**

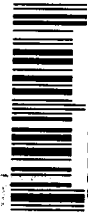
100 Tablets

NDC 55370-545-07

EXP. DATE:

ISSUED 5/96

9 1997



N 3 55370-545-07 2

LOT #:

6239460MV

Each tablet contains 800 mg acyclovir, USP.

USUAL DOSAGE: See package circular for full prescribing information. Dispense in a tight, light-resistant container, as defined in the USP.

Store between 15° and 25° C (59° and 77° F). Protect from light and moisture.

Manufactured for:

Aesgen_{INC}
Wilmington, NC 28403

By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

A

ACYCLOVIR Tablets

800 mg

**CAUTION: Federal law prohibits
dispensing without prescription.**

500 Tablets

NDC 55370-545-08

EXP. DATE:

ISSUED 5/96

6239300MV



N 3 55370-545-08 9

LOT #:

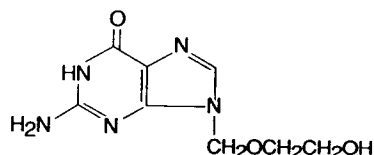
1 9 1997

ACYCLOVIR TABLETS



635402MV

DESCRIPTION: Acyclovir is an antiviral drug. The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one; it has the following structural formula:



Acyclovir is a white to off-white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$; and a molecular weight of 225.21. The maximum solubility in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25.

Each tablet for oral administration contains 400 mg or 800 mg of acyclovir. In addition, each tablet contains the following inactive ingredients: magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

VIROLOGY: Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity is against HSV-1, followed in decreasing order of potency against HSV-2 and VZV.

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. *In vitro*, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in three ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the *in vitro* susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

Drug Resistance: Resistance of VZV to antiviral nucleoside analogues can result from qualitative or quantitative changes in the viral TK or DNA polymerase. Clinical isolates of VZV with reduced susceptibility to acyclovir have been recovered from patients with AIDS. In these cases, TK-deficient mutants of VZV have been recovered.

Resistance of HSV to antiviral nucleoside analogues occurs by the same mechanisms as resistance to VZV. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase

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CLINICAL PHARMACOLOGY: Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table 1.

Table 1:
Acyclovir Pharmacokinetic Characteristics (Range)

Parameter	Range
Plasma protein binding	9% to 33%
Plasma elimination half-life	2.5 to 3.3 hr
Average oral bioavailability	10% to 20%*

*Bioavailability decreases with increasing dose.

In one multiple-dose, cross-over study in healthy subjects (n=23), it was shown that increases in plasma acyclovir concentrations were less than dose proportional with increasing dose, as shown in Table 2. The decrease in bioavailability is a function of the dose and not the dosage form.

Table 2:
Acyclovir Peak and Trough Concentrations
at Steady State

Parameter:	200 mg	400 mg	800 mg
C_{max}^{ss}	0.83 mcg/mL	1.21 mcg/mL	1.61 mcg/mL
C_{trough}^{ss}	0.46 mcg/mL	0.63 mcg/mL	0.83 mcg/mL

There was no effect of food on the absorption of acyclovir (n=6); therefore, acyclovir tablets may be administered with or without food.

The only known urinary metabolite is 9-[(carboxymethoxy)methyl]guanine.

Special Populations: Adults with Impaired Renal Function: The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Pediatrics: In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m² and 600 mg/m² in pediatric patients ages 7 months to 7 years was 2.6 hours (range 1.59 to 3.74 hours).

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase acyclovir half-life and systemic exposure. Urinary excretion and renal clearance were correspondingly reduced.

Clinical Trials: Initial Genital Herpes: Double-blind, placebo-controlled studies have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection and duration of lesion healing. The duration of pain and new lesion formation was decreased in some patient groups.

Recurrent Genital Herpes: Double-blind, placebo-controlled studies in patients with frequent recurrences (six or more episodes per year) have shown that daily administered acyclovir given daily for 4 months to 10 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of patients who received acyclovir 400 mg twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the patients showed that 71% to 87% were recurrence-free in each quarter.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, acyclovir (800 mg five times daily for 10 days) shortened the times to lesion scab-

3

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Herpes Zoster Infections: In a double-blind, placebo-controlled study of immunocompetent patients with localized cutaneous zoster infection, acyclovir (800 mg five times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.

In a similar double-blind, placebo-controlled study, acyclovir (800 mg five times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).

Treatment was begun within 72 hours of rash onset and was most effective if started within the first 48 hours.

Adults greater than 50 years of age showed greater benefit.

Chickenpox: Three randomized, double-blind, placebo-controlled trials were conducted in 993 pediatric patients ages 2 to 18 years with chickenpox. All patients were treated within 24 hours after the onset of rash. In two trials, acyclovir was administered at 20 mg/kg four times daily (up to 3,200 mg per day) for 5 days. In the third trial, doses of 10, 15, or 20 mg/kg were administered four times daily for 5 to 7 days. Treatment with acyclovir shortened the time to 50% healing, reduced the maximum number of lesions, reduced the median number of vesicles, decreased the median number of residual lesions on day 28, and decreased the proportion of patients with fever, anorexia, and lethargy by day 2. Treatment with acyclovir did not affect varicella-zoster virus-specific humoral or cellular immune responses at 1 month or 1 year following treatment.

INDICATIONS AND USAGE: Herpes Zoster Infections: Acyclovir is indicated for the acute treatment of herpes zoster (shingles).

Genital Herpes: Acyclovir is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes.

Chickenpox: Acyclovir is indicated for the treatment of chickenpox (varicella).

CONTRAINDICATIONS: Acyclovir is contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulations.

WARNINGS: Acyclovir tablets are intended for oral ingestion only.

PRECAUTIONS: Dosage adjustment is recommended when administering acyclovir to patients with renal impairment (see **DOSAGE AND ADMINISTRATION**). Caution should also be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction and/or the risk of reversible central nervous system symptoms such as those that have been reported in patients treated with intravenous acyclovir.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Herpes Zoster: There are no data on treatment initiated more than 72 hours after onset of the zoster rash. Patients should be advised to initiate treatment as soon as possible after a diagnosis of herpes zoster.

Genital Herpes Infections: Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is

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Genital Herpes Infections: Patients should be informed that acyclovir is not a cure for genital herpes. There are no data evaluating whether acyclovir will prevent transmission of infection to others. Because genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of a genital herpes recurrence is indicated, patients should be advised to initiate therapy at the first sign or symptom of an episode.

Chickenpox: Chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity. Adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course.

Drug Interactions: See **CLINICAL PHARMACOLOGY: Pharmacokinetics**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally six times a day (dosing appropriate for treatment of herpes zoster) or 200

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mg given orally six times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. Maximum plasma concentrations were three to six times human levels in the mouse bioassay and one to two times human levels in the rat bioassay.

Acyclovir was tested in 16 genetic toxicity assays. No evidence of mutagenicity was observed in four microbial assays. Acyclovir demonstrated mutagenic activity in two *in vitro* cytogenetic assays (one mouse lymphoma cell line and human lymphocytes). No mutagenic activity was observed in five *in vitro* cytogenetic assays (three Chinese hamster ovary cell lines and two mouse lymphoma cell lines).

A positive result was demonstrated in one of two *in vitro* cell transformation assays, and morphologically transformed cells obtained in this assay formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. No mutagenic activity was demonstrated in another, possibly less sensitive, *in vitro* cell transformation assay.

Acyclovir was clastogenic in Chinese hamsters at 380 to 760 times human dose levels. In rats, acyclovir produced a non-significant increase in chromosomal damage at 62 to 125 times human levels. No activity was observed in a dominant lethal study in mice at 36 to 73 times human levels.

Acyclovir did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study, they were 8 to 15 times human levels. At higher doses (50 mg/kg/day, s.c.) in rats and rabbits (11 to 22 and 16 to 31 times human levels, respectively) implantation efficacy, but not litter size, was decreased. In a rat peri- and post-natal study at 50 mg/kg/day, s.c., there was a statistically significant decrease in group mean numbers of corpora lutea, total implantation sites, and live fetuses.

No testicular abnormalities were seen in dogs given 50 mg/kg/day, i.v. for 1 month (21 to 41 times human levels) or in dogs given 60 mg/kg/day orally for 1 year (six to 12 times human levels). Testicular atrophy and aspermatogenesis were observed in rats and dogs at higher dose levels.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test, rats were given three s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. In this test, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.

There are no adequate and well-controlled studies in pregnant women. A prospective epidemiological registry of acyclovir use during pregnancy has been ongoing since 1984. As of June 1996, outcomes of live births have been documented in 494 women exposed to systemic acyclovir during the first trimester of pregnancy. The occurrence rate of birth defects approximates that found in the general population. However, the small size of the registry is insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of acyclovir in pregnant women and their developing fetuses. Acyclovir should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Acyclovir should be administered to a nursing mother with caution and only when indicated.

Geriatric Use: Clinical studies of acyclovir did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased renal function, and of concomitant disease or other drug therapy.

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Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS: Herpes Simplex: Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with acyclovir 200 mg administered orally five times daily every 4 hours for 10 days were nausea and/or vomiting in 8 of 298 patient treatments (2.7%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) two times daily for 1 year in 586 patients treated with acyclovir were nausea (4.8%) and diarrhea (2.4%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), and headache (2.2%).

Herpes Zoster: The most frequent adverse event reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir five times daily for 7 to 10 days in 323 patients was malaise (11.5%). The 323 placebo recipients reported malaise (11.1%).

Chickenpox: The most frequent adverse event reported during three clinical trials of treatment of chickenpox with oral acyclovir at doses of 10 to 20 mg/kg four times daily for 5 to 7 days or 800 mg four times daily for 5 days in 495 patients was diarrhea (3.2%). The 498 patients receiving placebo reported diarrhea (2.2%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE: Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects. Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION: Acute Treatment of Herpes Zoster: 800 mg every 4 hours orally, five times daily for 7 to 10 days.

Genital Herpes: Treatment of Initial Genital Herpes: 200 mg every 4 hours, five times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg two times daily for up to 12 months, followed by re-evaluation. Alternative regimens have included doses ranging from 200 mg three times daily to 200 mg five times daily.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir.

Intermittent Therapy: 200 mg every 4 hours, five times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days.

Intravenous acyclovir is indicated for the treatment of varicella zoster infections in immunocompromised patients.

When therapy is indicated, it should be initiated at the earliest sign or symptom of chickenpox. There is no information about the efficacy of therapy initiated more than 24 hours after onset of signs and symptoms.

Patients With Acute or Chronic Renal Impairment: In patients with renal impairment, the dose of acyclovir capsules and tablets should be modified as shown in Table 3:

Table 3: Dosage Modification for Renal Impairment

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m ²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.

Bioequivalence of Dosage Forms: Acyclovir suspension was shown to be bioequivalent to acyclovir capsules (n=20) and one acyclovir 800 mg tablet was shown to be bioequivalent to four acyclovir 200 mg capsules (n=24).

HOW SUPPLIED: Acyclovir Tablets (white, oval, unscored) containing 800 mg acyclovir and engraved with "A03" on one side and "800" on the other side. Bottle of 100 (NDC 55370-545-07), and bottle of 500 (NDC 55370-545-08).

Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

Acyclovir Tablets (white, oval, unscored) containing 400 mg acyclovir and engraved with "A02" on one side and "400" on the other side. Bottle of 100 (NDC 55370-544-07), and bottle of 1000 (NDC 55370-544-09). Store between 15° and 25°C (59° and 77°F) and protect from light and moisture.

CAUTION: Federal law prohibits dispensing without prescription.

Dispense in a tight, light-resistant container, as defined in the USP.

Manufactured by:

MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

For:

Aesgen, Inc.
Wilmington, NC 28403

Item # 635402MV

Revised 09/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074946

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA 74-946

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
5051 New Centre Drive
Wilmington, NC 28403

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies, that to the best of its knowledge, U.S. Patent No. 4,199,574 expired on April 22, 1997, and the product is not covered by any exclusivity provisions. The applicant will not market the product before April 22, 1997.

Innovator: Glaxo Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm: 8/19/96 - Original.
10/10/96 - Response to comments.
4/22/97 - Response to Bio. def. letter.
5/7/97 - Response to 1st def. letter (chem. & labeling).
6/17/97 - Response to 2nd def. facsimile (chem. & labeling). Subject of this review.
8/7/97 - Response to 3rd def. facsimile (labeling). Subject of this review.
9/30/97 - Response to 4th def. facsimile (labeling). Subject of this review.

FDA: 9/26/96 - Phone memo.
10/8/96 - Acknowledgment, with comments.
1/27/97 - Bio. def. letter.
3/5/97 - 1st def. letter (chem. & labeling).
5/30/97 - 2nd def. facsimile (labeling).
6/6/97 - 2nd def. facsimile (chem.).
6/24/97 - Bio. review, acceptable.
6/30/97 - Bio. letter, no further questions.
7/25/97 - 3rd def. facsimile (labeling).
9/4/97 - 4th def. facsimile (labeling).

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
R

12. RELATED IND/NDA/DMF(s)

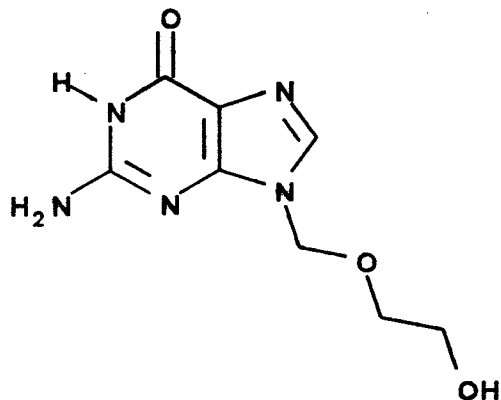
(b)4 - Confidential Business

13. DOSAGE FORM
Tablet

14. POTENCIES
400 mg & 800 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
 $C_8H_{11}N_5O_3$; M.W. = 225.21



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Response to Bio. letter assigned to Moheb Makary on 5/8/97.
DMF, EER, labeling, and method validation acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
6/24/97 (Chem.)
10/7/97 (labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074946

BIOEQUIVALENCE REVIEW(S)

Applied Analytical Industries, Inc.
Attention: Jennifer Huchison, RAC
Agent for: Aesgen, Inc.
5051 New Centre Dr.
Suite 103
Wilmington, NC 28403
|||||

Dear Madam:

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

Not less than (b)4(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 24 1997

UN

Acyclovir
400 mg and 800 Tablets
ANDA 74-946
Reviewer: Moheb H. Makary
WP 74946SDW.497

Aesgen Inc.
Wilmington, NC
Submission Date:
April 4, 1997

22

Review of An Amendment to Bioequivalence Studies,
Dissolution Data and Waiver Request

Objective:

The firm has replied to the reviewer's comments made in the review of the August 19, 1996 submission (bioequivalence studies on Acyclovir 800 mg Tablet, dissolution data and waiver request).

Comment #1

(b)4 - Confidential Business

Reply to Comment #1

The firm's response to the comment is acceptable.

Comment #2

(b)4 - Confidential Business

Recalculations of AUC(0-t) and AUCinf were carried out by the firm. The data was statistically reanalysed based on the new LOD of 25 ng/mL. After using an LOD of 25 ng/mL, the resulting 90% confidence intervals for the fasting study are as following:

LnAUC(0-t)	80.8-115.1%
LnAUCinf	82.3-115.7%
LnCmax	84.6-114.2%

All confidence intervals remain within the acceptable 80-125% range. The resulting ratios of the arithmetic and geometric means for Acyclovir under nonfasting conditions are as following:

B/C Arithmetic Mean	B/C Geometric Mean
0.93	0.90
0.94	0.90
0.85	0.87

The ratios of the least squares arithmetic and geometric means remain within 0.8-1.2 range for AUC(0-t), AUCinf and Cmax.

Reply to Comment #2

The firm's response to the comment is acceptable.

Comment #3

The firm was asked to clarify the discrepancies found for some subjects in the values of acyclovir AUC(0-t) and AUCinf between the hard copies (the jackets) and the diskettes in the fasting and nonfasting studies.

After its reanalysis of the data, the firm submitted new data diskettes for each study along with the hard copies. There are no discrepancies between the new data diskettes and the hard copies.

Reply to Comment #3

The firm's response to the comment is acceptable.

Recommendations:

1. The bioequivalence studies conducted by Aesgen, Inc., under fasting and nonfasting conditions on its Acyclovir, 800 mg Tablet, lot #MNT1581, comparing it to Glaxo-Wellcome's Zovirax^R 800 mg Tablet have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Aesgen's Acyclovir Tablet, 800 mg, is bioequivalent to Glaxo-Wellcome's Zovirax^R 800 mg Tablet.

2. The dissolution testing conducting by Aesgen, Inc., on its Acyclovir, 400 mg and 800 mg Tablets, lot #MNT1571 and lot #MNT1581, respectively, has been found acceptable by the Division of Bioequivalence. The formulation for the 400 mg strength is proportionally similar to the 800 mg strength of the test product which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 400 mg tablet of the test product is granted. The Division of Bioequivalence deems Acyclovir Tablet, 400 mg, manufactured by Aesgen Inc., to be bioequivalent to Zovirax^R Tablet, 400 mg, manufactured by Glaxo-Wellcome.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

/S/

Date: 6/9/97

/S/

Concur: _____

Date: 6/24/97

fr Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

MMakary/6-5-97 wp 74946SDW.497

cc: ANDA #74-946, original, HFD-650 (Director), HFD-658 (Makary), Drug File, Division File.

ACYCLOVIR 800 MG TABLET FASTING (655-95)

Table 4 : Mean Concentration (Untransformed) by Sampling Time

Sample Time	Collection (Hour)	Least Squares Means		Significance *
		Generic	Reference	
1	-0.5	0.000	0.000	0.0001
2	0.25	32.993	55.022	0.1762
3	0.5	271.524	313.752	0.5214
4	0.75	514.773	527.605	0.8340
5	1	622.957	685.638	0.3490
6	1.33	717.892	804.228	0.3031
7	1.67	742.598	830.163	0.3346
8	2	760.276	853.490	0.2888
9	2.5	785.904	780.606	0.9537
10	3	676.007	700.503	0.7668
11	4	528.904	556.467	0.7141
12	6	276.000	295.572	0.6032
13	8	163.986	171.689	0.7112
14	10	104.297	108.736	0.6790
15	12	73.921	72.843	0.9028
16	16	47.736	46.503	0.7541
17	24	28.526	22.983	0.3631

* Comparisons computed by estimate command in GLM procedure.

ACYCLOVIR 800 MG TABLET FED/FAST (654-95)

Table 4 : Mean Concentration of Acyclovir (Untransformed) by Sampling Time

Sample Time	Collection (Hour)	Least Squares Means			Significance *	
		Generic Fed	Generic Fast	Reference Fed	Generic Fed & Generic Fast	Generic Fed & Reference Fed
1	0	0.00	0.00	0.00	---	---
2	0.25	8.81	54.49	0.00	0.0308	None
3	0.5	54.76	351.99	64.46	0.0001	None
4	0.75	213.90	618.49	204.43	0.0001	None
5	1	384.06	804.62	371.88	0.0022	None
6	1.33	667.22	916.96	788.94	None	None
7	1.67	855.81	997.59	1025.08	None	None
8	2	945.34	1020.95	1166.19	None	None
9	2.33	983.99	1001.44	1184.22	None	None
10	2.67	1009.01	927.81	1141.37	None	None
11	3	990.52	851.56	1093.75	None	None
12	3.5	962.30	768.92	1003.84	None	None
13	4	898.19	651.98	982.49	0.0343	None
14	5	686.72	468.68	745.04	0.0216	None
15	6	506.01	330.43	531.78	0.0109	None
16	8	287.03	198.92	292.94	0.0144	None
17	10	182.27	126.97	178.39	0.0132	None
18	12	110.75	87.23	111.67	None	None
19	16	56.54	40.48	52.61	0.0138	None
20	24	15.58	7.47	10.13	None	None

* Comparisons computed by estimate command in GLM procedure.

1/14
JAN 7 1997

Acyclovir
400 mg and 800 Tablets
ANDA 74-946
Reviewer: Moheb H. Makary
WP 74946SDW.896

Aesgen Inc.
Wilmington, NC
Submission Date:
August 19, 1996

Review of Two Bioequivalence Studies, Dissolution Data
and Waiver Request

I. Objective:

The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its Acyclovir 800 mg tablets and dissolution data to compare the test product relative to Zovirax[®] (Glaxo-Wellcome) 800 mg tablets for review. The firm has also requested a waiver of in vivo bioequivalence study requirements for its 400 mg strength. The formulations for the drug products Acyclovir 800 mg and 400 mg tablets were also submitted.

II. Background:

Acyclovir is 9-[(2-hydroxyethoxy)methyl]guanine, a synthetic purine nucleoside with antiviral activity against human herpes viruses, including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). The viral inhibitory activity is highly selective, involving preferential uptake into virus-infected cells and requiring a virus-specific thymidine kinase for conversion to the monophosphate. Subsequent conversion to the triphosphate results in irreversible binding to DNA polymerase and termination of DNA replication. Acyclovir capsules, tablets and suspension are indicated for the treatment of initial episodes and management of recurrent episodes of genital herpes in certain patients and for the acute treatment of herpes zoster and chicken pox.

Acyclovir is marketed as Zovirax (Glaxo-Wellcome) 200 mg capsules (NDA #18-828, 1/25/85), 800 and 400 mg tablets (NDA #20-089, 4/30/91), and oral suspension 200 mg/5 mL (NDA #19-909, 12/22/89).

Pharmacokinetics

The oral absorption of acyclovir is slow, variable, and incomplete,

with absolute bioavailability estimated as 15-30% from different studies involving both normals and patients. Reported values for C_{max} and T_{max} in healthy subjects after a 200 mg capsule were 0.3 ± 0.1 mg/L and 1.5-2.5 hours, respectively. Several studies in healthy volunteers have demonstrated dose-dependent absorption: (1) fraction of the dose recovered unchanged in the urine decreased over the dosing range of 100-600 mg (13.2% of a 100 mg dose; 12.1%, 200 mg; 7.4%, 400 mg; 6%, 600 mg dose); (2) mean C_{max} was 0.58 mg/L after a single 600 mg dose and 0.50 mg/L after a single 200 mg dose; (3) mean AUC after a 600 mg dose given as divided doses every four hours, was about three times higher than after a single 600 mg dose; and (4) mean AUC from a 400 mg dose given as a duodenal infusion was about 1.7 times that from tablets, which suggested capacity-limited absorption. However, the results of one multiple dose study (200 mg q4h vs. 3 X 200 mg q4h) in immunocompromised patients suggested that net absorption of acyclovir is nearly proportional to dose in the 200-600 mg dose range.

Plasma elimination of acyclovir is biphasic with a beta phase half-life of 2-3 hours. Renal excretion is the major route of elimination with 45-79% of a dose recovered unchanged in the urine. After an intravenous infusion of a ^{14}C tracer dose in patients, 71-99% of the dose was recovered in the urine. There is only one significant, inactive metabolite, 9-carboxymethoxymethyl guanine (CMMG), which accounts for 8-14% of a dose.

III. Study/Protocol #655-95 For Single-dose Fasting
Bioequivalence Study:

Study site:

(b)4 - Confidential Business

Analytical site:

Study design:

A randomized, single-dose, open-label, 2-way crossover bioequivalence study under fasting conditions.

Study dates:

April 26, 1996

May 5, 1996

Subjects:

Twenty (26) normal healthy subjects (10 female, 16 male) enrolled in the study. All met the selection criteria described in the protocol. They were judged to be healthy based on medical history, physical examination and clinical laboratory tests within 14 days prior to period 1 dosing. All subjects were within 20 to 42 years of age and the weight range was not more than $\pm 15\%$ for height and body frame as per Desirable Weights for Men - 1983 Metropolitan Height and Weight Table. One of the subjects withdrew before the conclusion of the study, and therefore their data was not included in the analysis. Twenty-five (25) subjects completed the study (9 female, 16 male).

Exclusion criteria:

- a. Volunteers with a recent history of drug or alcohol addiction or abuse.
- b. Volunteers with the presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system or psychiatric disease.
- c. Volunteers demonstrating a positive hepatitis B surface antigen screen HIV 1 & 2 antibody screen.
- d. Volunteers with a history of allergic response to acyclovir or related drugs.
- e. Volunteers who report receiving any investigational drug within 60 days prior to period I.
- f. Any medication by prescription in past 14 days, except birth control pills.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 1x800 mg Acyclovir Tablets (Aesgen), lot

#MNT1581, lot size (b)4 - tablets, Content uniformity and potency are 99.0% (%CV=0.8) and 99.0%, respectively.

Reference product: B. 1x800 mg Zovirax[®] Tablets (Glaxo-Wellcome), lot #502054, Exp. 5/97. Potency is 99.7%.

Food and fluid

intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. Water was permitted ad lib. until 1 hour before dosing and 2 hours after dosing. All subjects consumed 240 mL of water two hours after dosing.

Blood collection: Blood samples were drawn into Vacutainers containing EDTA prior to drug administration. Similarly, samples were drawn at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours. All blood samples were drawn at 1 minute intervals. Blood samples were centrifuged at 2700 RPM for 10 minutes.

Washout period: 7 days.

Assay Methodology:

Sensitivity:

Specificity:

(b)4 - Confidential Business

Precision:

Accuracy:

Stability:

(b)4 - Confidential Business

Analytical notes:

Statistical Analysis:

AUC(0-t), AUCinf, Cmax, Kel, T1/2 and concentrations at each sampling time point were determined for acyclovir. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for LnAUC(0-t), LnAUCinf and LnCmax.

IV. In Vivo Results:

Twenty-six (26) subjects enrolled and twenty-five (25) subjects completed the study. Subject #1 withdrew from the study due to flu-like symptoms following the period I dosing. The investigator determined the adverse event was not related to the study drug. However, the subject subsequently received treatment with antibiotics and withdrew from the study. Subject #24 experienced lightheadedness which was considered as a possibly related to the study drug.

The plasma concentrations and pharmacokinetic parameters for acyclovir are summarized below in Table I.

Table I

LSMs Plasma Acyclovir Concentrations and Pharmacokinetic
Parameters Following an Oral Dose of 1x800 Acyclovir
Tablets under Fasting Conditions
 (N=25)

	<u>Treatment A</u>	<u>Treatment B</u>
	Aesgen-Test	Glaxo-Wellcome
	Lot #MNT1581	Lot #502054
	ng/mL	ng/mL
<u>Time</u>		
hr		
-0.5	0	0
0.25	35.02	58.05
0.50	271.52	313.75
0.75	514.77	527.61
1.00	622.96	685.64
1.34	717.89	804.23
1.68	742.60	830.16
2.00	760.28	853.49
2.50	785.90	780.61
3.00	676.01	700.50
4.00	528.90	556.47
6.00	276.00	295.57
8.00	163.99	171.69
10.00	104.30	108.74
12.00	75.46	73.45
16.00	47.74	46.50
24.00	30.51	26.53

AUC(0-t) (ng.hr/mL)	4620.28	4846.44
AUCinf (ng.hr/mL)	4915.89	5080.25
Cmax (ng/mL)	941.94	971.17
Tmax (hr)	1.67	1.76

	<u>90% CI</u>
LnAUC(0-t)	81.2-113.7%
LnAUCinf	82.7-114.6%
LnCmax	84.6-114.2%

1. For Acyclovir, the least squares means AUC(0-t), Cmax and AUCinf values were 4.67%, 3.23% and 3.0% lower, respectively, for the test product than for the reference product. The differences are not statistically significant and the 90% confidence intervals for the above parameters are within the acceptable range of 80-125% for log-transformed data.

2. The Acyclovir mean plasma levels peaked at 2.00 and 2.5 hours for the reference and the test products, respectively, following their administration under fasting conditions.

3. The firm calculated AUC(0-t) and AUCinf from -0.5 hour to the last quantified sample. In addition, there are discrepancies for some subjects in the values of acyclovir AUC(0-t) and AUCinf between the hard copies (the jackets) and the diskettes in the above study.

V. Study #654-95 For Single-dose Post Prandial Bioequivalence Study of Acyclovir 800 mg Tablets

The objective of this study was to evaluate the effect of food on the rate and extent of absorption of a single dose of Acyclovir 800 mg Tablets (Aesgen) relative to Zovirax[®] 800 mg Tablets (Glaxo-Wellcome)

Study site:

(b)4 - Confidential Business

Analytical site:

Study design: Single-dose, three-way crossover, post-prandial bioequivalence study.

Study dates: 5/10/96 - 6/2/96

Subjects: Eighteen (18) healthy volunteers (3 female, 15 male) were enrolled in the study. All met the selection criteria described in the protocol. All eighteen subjects completed the entire clinical portion of the study.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: 1. 1x800 mg Acyclovir Tablets (Aesgen), lot #MNT1581, administered following an overnight fast.
2. 1x800 mg Acyclovir Tablets (Aesgen), lot #MNT1581, administered after a high fat breakfast preceded by an overnight fast.

Reference product: 3. 1x800 mg Zovirax^R Tablets (Glaxo-Wellcome), lot#502054, administered after a high fat breakfast preceded by an overnight fast.

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods. No fluid except that given with the standardized breakfast (1 fried egg, 1 serving of hashed browned potatoes, 1 slice Canadian bacon, 1 buttered English muffin, 1 slice American cheese, 8 ounces of whole milk and 6 ounces of orange juice) and with drug administration was allowed from 1 hour prior to dose administration until 2 hours after dosing. Four hours after dose, water was allowed ad lib, if requested, but was generally

controlled during confinement.

Blood collection: Blood samples were drawn into Vacutainers containing EDTA prior to drug administration. Similarly, samples were drawn at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, 16 and 24 hours.

Washout period: One week.

Assay Methodology: Same as in Study #655-95.

Statistical Analysis: Same as in Study #655-95.

VI. In Vivo Results:

Eighteen (18) subjects enrolled and completed the study. Three mild adverse events were reported during the study. The events were not considered related to the study drug. All the events were resolved, and none resulted in the withdrawal of any subject from the study.

The plasma concentrations and pharmacokinetic parameters for acyclovir are summarized below in Table II.

Table II

LSMs Plasma Acyclovir Concentrations and Pharmacokinetic
Parameters Following an Oral Dose of 800 Acyclovir
Tablet under Fasting and Nonfasting Conditions
(N=18)

<u>Treatment A</u>	<u>Treatment B</u>	<u>Treatment C</u>
Aesgen-Test	Aesgen-Test	Glaxo Wellcome-Reference
Lot #MNT1581	Lot #MNT1581	Lot #502054
Fasting	Nonfasting	Nonfasting
ng/mL	ng/mL	ng/mL
<u>Time</u>		
hr		

0	0	0	0
0.25	54.49	8.81	3.26
0.50	351.99	56.62	65.73
0.75	619.31	214.78	204.43
1.00	804.62	384.06	372.80
1.34	916.69	667.22	788.94
1.68	997.59	855.81	1025.08
2.00	1020.95	945.34	1166.19
2.34	1001.44	983.99	1184.22
2.68	927.81	1009.01	1141.37
3.00	851.56	990.52	1093.75
3.50	768.92	962.30	1003.84
4.00	651.98	898.19	982.49
5.00	468.68	686.72	745.04
6.00	330.43	506.01	531.78
8.00	198.92	287.03	292.94
10.00	126.97	182.27	178.39
12.00	87.23	111.95	111.67
16.00	41.21	57.36	53.85
24.00	12.11	17.76	15.38

	A	B	C	B/C
AUC(0-t) (ng.hr/mL)	5515.01	6369.37	6844.23	0.93
AUCinf (ng.hr/mL)	5681.72	6581.10	7016.56	0.94
Cmax (ng/mL)	1258.73	1292.11	1510.18	0.86
Tmax (hr)	1.89	2.57	2.77	

1. The acyclovir mean plasma levels peaked at 2.34 and 2.68 hours for the reference and test products, respectively, under nonfasting conditions and at 2 hours for the test product under fasting conditions.

2. For Aesgen's test product, the Least Squares Means AUC(0-t), AUCinf and Cmax values were 6.9%, 6.2% and 14.4% lower, respectively, than the reference product values under nonfasting conditions. The ratios of the test arithmetic LSM to the reference arithmetic LSM are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax.

3. For the comparison of the test product under fasting and nonfasting conditions, there was no indication of a food effect.

4. There are discrepancies for some subjects in the values of acyclovir AUC(0-t) and AUCinf between the hard copies (the jackets) and the diskettes in the above study.

VII. Formulations:

Aesgen's formulations for its Acyclovir 400 mg and 800 mg Tablets are shown in Table III.

VIII. In Vitro Dissolution Testing

Method: USP 23 apparatus 2 (paddle) at 50 rpm

Medium: 900 mL of water

Sampling Time: 15, 30, 45 and 60 minutes.

Test Product: Aesgen's Acyclovir Tablets

400 mg, lot #MNT1571

800 mg, lot #MNT1581

Reference

Product: Glaxo-Wellcome's Zovirax Tablets

400 mg, lot #4R2123

800 mg, lot #5020054

Number of

Tablets: 12

The dissolution testing results are shown in Table IV.

VIII. Deficiency Comments:

(b)4 - Confidential Business

(b)4 - Confidential Business

IX. Recommendations:

1. The bioequivalence studies conducted by Aesgen, Inc., under fasting and nonfasting conditions on its Acyclovir, 800 mg Tablets, lot #MNT1581, comparing it to Glaxo-Wellcome's Zovirax[®] 800 mg Tablets have been found incomplete for the reasons given in deficiency comments 1-4.
2. The dissolution testing conducting by Aesgen, Inc., on its Acyclovir, 400 mg and 800 mg Tablets, lot #MNT1571 and lot #MNT1581, respectively, has been found acceptable by the Division of Bioequivalence.
3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than (b)4 of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.
4. Waiver of the in vivo bioequivalence study requirements for the firm's Acyclovir, 400 mg Tablets can not be granted for the reasons given in deficiency comments 1-4.

The firm should be informed of the deficiency comments and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRI
FT INITIALLED RMHATRI

/S/

Date: 1/7/97

/S/

Concur: _____

Date: _____

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMakary/1-6-97 wp 74946SDW.896
cc: ANDA #74-946, original, HFD-658 (Makary), Drug File, Division
File.

Table IV. In Vitro Dissolution Testing

Drug (Generic Name): Acyclovir Tablets

Dose Strength: 400 mg and 800 mg

ANDA No.: 74-946

Firm: Aesgen, Inc.

Submission Date: August 19, 1996

File Name: 74946SDW.896

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 50

No. Units Tested: 12

Medium: 900 mL of water

Specifications: NLT (b)4 in 30 minutes

Reference Drug: Zovirax

Assay Methodology: (b)4

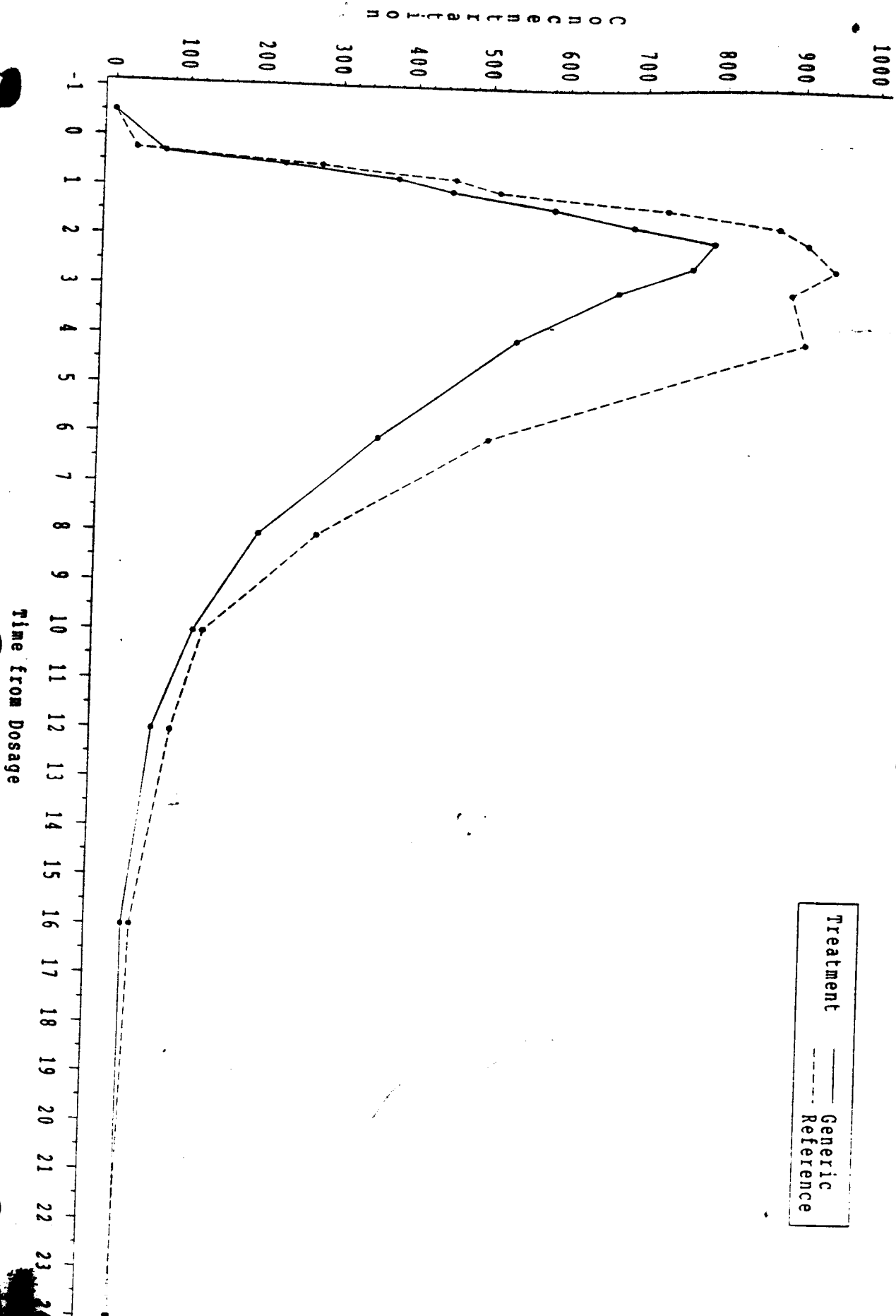
II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MNT1581 Tablet Strength(mg) 800			Reference Product Lot # 502054 Strength(mg) 800		
	Mean %	Range	%CV	Mean %	Range	%CV
15	79.3	(b)4 -	7.3	88.7	(b)4 -	2.9
30	93.7	Confidential	3.3	96.0	Confidential	2.1
45	99.7	Business	1.8	98.6	Business	1.3
60	100.5		0.8	99.8		1.3
Sampling Times (Minutes)	Test Product Lot # MNT1571 Tablet Strength(mg) 400			Reference Product Lot # 4R2123 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
15	84.8	(b)4 -	9.0	83.3	(b)4 -	3.7
30	94.7	Confidential	4.0	91.2	Confidential	1.9
45	98.1	Business	1.6	95.1	Business	2.4

60	99.6	■ (b)4 - ■	1.0	96.9	■ (b)4 - ■	1.9
					Confidential	

Acyclovir Two—May 800mg Tablet — Fasting

Concentration vs. Time
SUBJECT NUMBER=2



080

Acyclovir Three-Way 800mg Tablet - Fed/Fast

Mean Concentration vs. Time

